Reviewer's report

Title: Extrafine Beclomethasone/formoterol compared to Fluticasone/salmeterol Combination Therapy in COPD

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Reviewer: Marc Miravitlles

Reviewer's report:

The authors present the results of a RCT to compare BDP/FF and FP/S in patients with moderate to severe COPD. The data are new and the manuscript is overall well written, but some aspects need to be clarified.

1. Method. The inclusion criteria include an increase of at least 5% in FEV1 after bronchodilator. This is quite unusual, Why was this criterion included? In addition, patients had to have no more than 1 exacerbation within the previous year; this is promoting off label use of ICS, because their use is approved only in severe COPD AND exacerbations (despite what is written in the GOLD document). The authors should provide data on the percentage of patients without exacerbations the previous year in Table 1, together with some missing physiologic data, such as pre-FEV1 in % predicted, and more importantly, the reversibility of both groups of patients at baseline.

2. Study design. In the run-in the patients received ipratropium, but after randomisation only salbutamol was allowed as comedication. It is difficult to understand why they changed the short-acting BD in such a short period of time. Why not continue with ipratropium or, prescribing salbutamol during the run-in??

3. In Figure 1, it reads that 187 screening failures were due to ineligibility. This is not informative. What were the reasons for ineligibility?

4. It should be acknowledged that the symptoms questionnaire has not been validated for use in RCT. The questionnaire should be presented in the online supplement. Is there any information regarding symptoms in the morning?

5. Discussion. It reads that the results demonstrate that the lower dose of ICS provides equivalent symptom control. This cannot be conclude from the current study. There is no evidence that the symptom control is due to ICS and not to the LABA. It could also be concluded that the similar results for both combinations suggested that there is no effect at all from ICS irrespective of the dosis. Even more so for the comment on the suggested effect of lower dose of ICS on the improvement in exercise capacity. There is no evidence that ICS improves exercise capacity, but there is plenty of evidence on the improvement in exercise capacity with LABAs.

6. The Limitations section should mention the lack of a control group with LABA alone to really address the effect of adding ICS in this population of patients,
most being without a clear indication for long-term treatment with ICS.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

None